CASE 50.—Herbert T., aged fourteen years. September 26, 1911. Episcopal Hospital. Right, middle third. Dressed in full supination. Examined January 21, 1912. Some callus palpable. Right forearm: supination, —10 degrees; pronation, 155 degrees. Left forearm: supination, —10 degrees; pronation, 140 degrees. Class I.

CASE 51.—John D., aged eighteen years. October 10, 1911. Episcopal Hospital. Right, junction of middle and upper third. Full supination. Some projection of upper fragment of radius on flexor surface. Examined January 28, 1912. Slight callus of radius. Right forearm: supination, 40 degrees; pronation, 135 degrees. Left forearm: supination, —5 degrees; pronation, 120 degrees. Class III. (This patient was under the care of the writers only seventeen days.)

CASE 52.—Stanley C., aged fourteen years. October 10, 1911. Episcopal Hospital. Left, lower third of radius, and through lower epiphysis of ulna. Full supination. Examined January 27, 1912. Left forearm: supination —15 degrees; pronation, 160 degrees. Right forearm: supination, —5 degrees; pronation, 160 degrees. Class I.

FURTHER EVIDENCE IN SUPPORT OF THE TOXIC PATHOGENESIS OF BRONCHIAL ASTHMA, BASED UPON EXPERIMENTAL RESEARCH.

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IN 1905, in a paper before the Orleans Parish Medical Society,[1] I called the attention of the profession to the importance of a consideration of the role played by intestinal toxins in producing various pathological conditions. Since then I have given the matter special attention, and I had already collected several cases of bronchial asthma, associated with intestinal toxins, which were relieved by abolishing the intestinal toxemia, when Rochester[2] read his paper in 1906, before the Section on Medicine of the American Medical Association. The discussion following this paper showed that the general opinion of the profession was opposed to the toxic pathogenesis of asthma. In 1909, before the Louisiana State Medical Society,[3] I reported several cases of bronchial asthma relieved entirely along dietetic lines by relieving the associated toxemia of intestinal origin; but discussion by Dock and others again revealed the fact that the profession was not as yet prepared to accept the toxemic basis of this symptom.

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[1] Proceedings Orleans Parish Medical Society, 1905.

[2] Jour. Amer. Med. Assoc., 1906, xlvii, 1983.

Since first becoming interested in the subject, I have collected histories of 121 cases of spasmodic bronchial asthma, partly my own and partly from other clinicians, which were associated with an intestinal toxemia, and were relieved by relieving this latter condition.

While I am not prepared, as yet, to claim that every case of asthma is due to a special toxin of intestinal origin and produced by the putrefaction of proteid material, I have yet to see one case in which, in my opinion, it is not the underlying cause.

Bouchard,[4] nearly twenty years ago, in speaking of paroxysmal attacks of asthma, states: "These, also, I suspect, we must rather consider the result of the elimination of toxic substances than a reflex act." However, in reading the literature pertaining to this so-called disease, one is struck by the various hypotheses expounded as to its etiology. Saenger[5] believes the underlying cause is an inherited "neurosis," with a mechanical obstruction superinduced by bronchial catarrh, and his treatment consists in relieving the latter condition by inhalations, etc.

Goldschmidt[6] also presupposes an hereditary neurosis, and classifies asthma into: (1) "Ein asthma epilepticum s. nervosum; (2) ein asthma bronchiale s. catarrhale paroxysmale; (3) ein asthma catarrhale chronicum; (4) ein asthma catarrhale permanens."

However, he recognizes: (1) "Ein asthma toxicum (aetiologische); (2) ein asthma catarrhale (anatomische); (3) ein asthma reflexivum (physiologische)."

He considers that the disease can best be classified according to its associated symptomatology, but in his toxic type he apparently considers that carbon dioxide poisoning of the blood stimulates the respiratory centre, resulting in the bronchial spasm, and does not mention the likelihood of intestinal toxins playing any important role. This view, to me, is untenable, after reviewing the recent work on the physiology of the respiratory centre carried on by Henderson[7] and others.

Bergmann[8] classifies asthma into: (1) A traumatic asthma, caused by stimulation of the respiratory centre through trauma to the cerebrum or medulla, as well as through a psychical defect

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[3] Proceedings Louisiana State Medical Society, 1909.

[4] Lectures on Auto-intoxication in Disease, 1894, p. 171.

[5] Ueber Asthma und seine Behandlung, Berlin, 1910.

[6] Asthma, Munich, 1910.

[7] Johns Hopkins Hosp. Bull., xxi, 1910, 233.

[8] Das Asthma, sein Wesen und sein Behandlung, Wiesbaden, 1910, p. 36.

(2) A reflex asthma, caused by stimulation of the respiratory centre, through abnormalities in the various mucous membranes, as well as through a reflex stimulation of the respiratory centre through the central organism itself, as in so-called neurasthenia. (3) A toxic asthma, caused by the stimulation of the respiratory centre through the toxic condition of the blood.

Many other classifications are proposed, such as teeth asthma, supposed to be caused by defective teeth; dyspeptic asthma; and sexual asthma, especially advocated by Sadger,[9] a pupil of Freud.

The various classifications will continue to grow as long as we regard asthma as a distinct disease, instead of as a symptom of some other underlying constitutional condition.

The few reports of postmortem sections of patients dying in attacks of asthma, which I have been able to find in the literature,[10] are so widely at variance that no definite idea can be formed as to the pathology of this condition, further pointing to the fact that asthma should be classified as a symptom of an underlying constitutional pathological condition, associated sometimes with epilepsy, sometimes with cardiac disease, and at times, probably, with every disease known.

Hare[11] lays a great deal of stress upon the toxic basis of asthma, but his conclusions that it is brought on by "glycogenic distention of the liver," with resulting hypocarbonization of carbohydrates, is not based upon sound physiological facts, nor are his results in accord with my experience. More likely the engorgement of the liver of which he speaks allows the intestinal toxins to pass through into the general circulation without being synthesized, and their toxic action is thus manifested.

During the past summer and autumn, while working in Vienna with Prof. Karl von Noorden and Prof. Richard Kraus, I decided to attempt to prove or disprove our clinical deductions by animal gentlemen experimentation, and I wish to take this means of thanking these for their courtesy and assistance during my investigations and for their free provision of material.

The hypothesis put forward to prove was: "If asthma is caused by intestinal toxemia a definite toxin exists, which causes bronchial spasm similar in action to muscarin, and this toxin originates in the intestinal canal." In seeking this specific toxin, I was led to investigate the amins formed by intestinal putrefaction of the several amino-acids of normal pancreatic digestion of proteids, as I had long since satisfied myself by earlier chemical investigation and from the work of others, that the Charcot-Leyden crystals are amins closely allied to putrescin and cadaverin. On putrefaction the several amino-acids split off carbon dioxide and form their corresponding amins; so that we find a corresponding amin to leucin, tyrosin, arginin, histidin, and the other amino-acids formed in pancreatic digestion of proteids. The physiological action of the several amins have been excellently worked out by Barger and Dale,[12] and their results explain many of the clinical symptoms observable in cases of intestinal toxemia, although their work was carried on with a view to obtaining the active principles of ergot, adrenalin chloride, etc.

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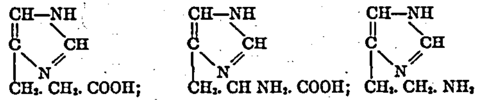
[9] Zentralbl. f. Psychoanalyse, 1911, Hefte 5 and 6, p. 200.

[10] Meeting held by the Militärärzlichen Gesellschaft, Berlin, 1886, p. 13; also see Berkart on Bronchial Asthma, its Pathology and Treatment, London, 1887; and Proceedings of the London Pathological Society, 1903.

[11] The Food Factor in Disease, London, 1905.

Of the several amins, betaimidazolylethylamin, while it has a slight action on the blood pressure, has a specific action on unstriped muscle tissue, causing contraction of the uterus as well as a contraction of the bronchioles, resulting in great dyspnea and death in the rabbit and guinea-pig, from complete occlusion of air by the tonic spasm of the bronchioles. The isolation of this amin and its physiological action was accidently discovered by Barger and Dale while investigating the action of ergot on the uterus. About the same time Kutscher[13] discovered a base in extract of ergot which had the same action on the bronchioles. Ackermann,[14] we find, was able to obtain the base by the putrefaction of histidin, while Windhaus and Voigt,[15] in 1907, were able to obtain it synthetically from imidazolylproprionic acid, according to the following steps:


Imidazolylpropionic acid. Histidin. Betaimidazolylethylamin.

Barger and Dale[16] were later able to obtain this base from an extract of the intestinal mucosa of the ox, indicating that the base is absorbed by this means from the intestinal canal. The experiments carried on by Dale and Laidlaw[17] to determine its physiological action were made with the base separated by them from ergot and from the intestinal mucosa, with the synthetic substance of Windhaus and Voigt[18] and with the base of Ackermann and Kutscher,[19] as well as with some of the base obtained by the putrefaction of histidin, the actions of which were all similar; so that their results can safely be accepted as representing the physiological action of betaimidazolylethylamin.

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[12] Jour. Phys., 1910, xli, 1 and 2, 19.

[13] Zentralbl. f. Physiol., 1910, xxiv, 163.

[14] Zeit. f. phys. Chem., 1910, Band lxv, 504.

[15] Bericht des Deut. Gesellschaft, 1907, xl, 3691.

[16] Jour. Phys., 1910, xli, 494, No. 6.

[17] Ibid., 318, No. 5.

[18] Loc. cit.

[19] Zeit. f. Biol., 1910, Band liv, p. 387

Through the courtesy of Dr. Dale, I was able to obtain a large supply of the base for experimental purposes, and in this preliminary paper only a summary of the experimental work can be given, the details of which will appear in a later article, after a few further experiments have been completed. I obtained the identical results as Dale and Laidlaw,[20] namely, contraction of the uterus and bronchioles by intravenous injection, resulting in death from half a milligram in the guinea-pig, the animal dying in six minutes, with violent inspiratory efforts, the heart continuing to beat long after respiration had ceased. At post mortem the lungs were found pale and enormously distended and protruding from the thorax after section (Fig. 1). The spasm is so intense that when connected with a Meyer artificial respiration pump, no air can be forced in or drawn out of the lungs, the organ remaining permanently distended, as seen in anaphylaxis. In addition, I found that the same dose administered into the trachea causes identical bronchial phenomena, while subcutaneous and intraperitoneal injections are much less toxic, suggesting that the action is entirely local on the unstriped muscle fiber and that the subcutaneous tissues have a detoxicating effect. Its action upon blood pressure and upon the uterus is not pertinent to the present subject, and I would refer anyone interested in this particular point to the paper by Dale and Laidlaw.[21]

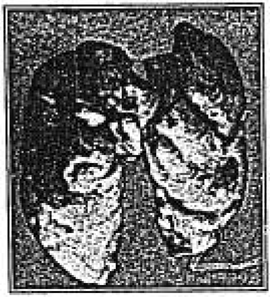

FIG. 1.—Photograph of guinea-pig lungs after intravenous injection of 0.5 milligram of beta-imidazolylethylamin. Dark portions show normal lung tissue. Lighter portions are emphysematous.

Attempts so far to isolate the base from the blood of asthmatics have been unsuccessful, due to the many precipitations and filtrations; but experiments now in progress, I have reason to believe, will result in this being accomplished. However, I was able to isolate the base by Kutscher's method from three specimens of feces, but was unsuccessful in twelve other specimens, suggesting that the presence of the base in intestinal contents will vary according to diet and probably also with varying intestinal flora.

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[20] Loc cit.

[21] Loc cit.

Injections of the urine of asthmatics, as well as the urine of normal guinea-pigs and rabbits, cause the characteristic bronchial spasm and death, with the characteristic postmortem appearance of the lungs above referred to (Fig. 2). The appearance of the lungs and the symptoms of the animal are similar to those dying from an anaphylactic shock, recalling the opinion of Meltzer[22] that asthma is a condition of anaphylaxis. The delayed coagulation of the blood and the continuous fall of blood pressure observable in anaphylaxis is not found, however, after injections of betaimidazolylethylamin, although a lowered body temperature was uniformly observed.

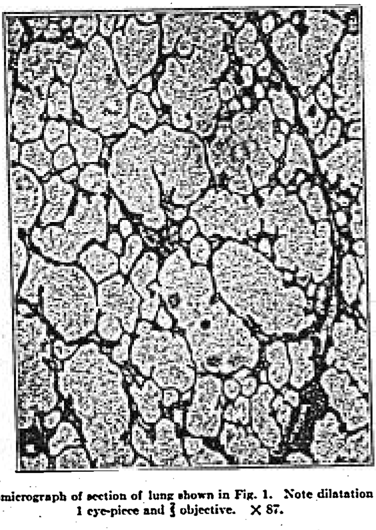

FIG. 2.—Photomicrograph of section of lung shown in Fig. 1. Note dilatation of air vesicles. 1 eye-piece and ⅔ objective. × 87.

However, no one has as yet fully explained the phenomena of anaphylactic shock, and it is possible that in injecting a foreign serum a mixture of nitrogenous toxic bases is also injected, which is ordinarily detoxicated, but which are not detoxicated by the tissues on the second injection of serum owing to the previous injection having exhausted this hypothetical detoxicating substance. From experiments, details of which will appear later, it appears that the normal human being, as well as the cat and dog, have the power of detoxicating not only betaimidazolylethylamin but also the other toxic amins formed by intestinal putrefaction, while the asthmatic individual has apparently lost this power.

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[22] Jour. Amer. Med. Assoc., 1910, lv, 1021–1024.

We are accustomed to notice urticaria as evidence of intestinal toxemia, while the eosinophilia in asthma and anaphylaxis are frequent accompaniments of intestinal toxemia.

In my paper before the Louisiana State Medical Society in 1909, already referred to, I stated: "The fact that I have found evidence of auto-intoxication in every case of asthma examined by me for four years, leads me to believe that during the attack there is some toxin in the blood which acts similarly to the muscarin, or which depresses the respiratory centre to such an extent that the reflex stimulation of an inflamed nasal mucosa results in stimulation of the constrictor fibers of the vagus."

I now submit the above facts as bearing out, in part, my original contention, which I hope to be able to prove definitely in a short time by the isolation of this specific amin from the blood of asthmatics.

In closing, I wish to thank Dr. Maurice Couret, of the pathological department of Tulane University, for his kindness in taking the accompanying photographs.

A RECURRENT DISEASE OF THE SKIN ASSOCIATED WITH HIGH WINDS AND COLD WEATHER, FOR WHICH THE NAME DERMATITIS HIEMALIS HAS BEEN PROPOSED.

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The skin from its exposed condition is more influenced by extraneous conditions, such as climate, etc., than are other organs of the body. Many diseases of the skin are limited to certain